

FORM PTO-1390 (REV. 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			4013-0158P
INTERNATIONAL APPLICATION NO. PCT/SE99/01729			U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>09/800455</b>
INTERNATIONAL FILING DATE September 29, 1999		PRIORITY DATE CLAIMED October 2, 1998	
TITLE OF INVENTION BIOACTIVE COMPOSITE MATERIALS AND METHOD OF PRODUCING THE SAME			
APPLICANT(S) FOR DO/EO/US ADOLFSSON, Erik; HERMANSSON, Leif			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<p>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).</p> <p>4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <p>a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</p> <p>b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. WO 00/19965</p> <p>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <p>a. <input type="checkbox"/> is transmitted herewith.</p> <p>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4)</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</p> <p>b. <input type="checkbox"/> have been transmitted by the International Bureau.</p> <p>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</p> <p>d. <input checked="" type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>			
Items 11. to 20. below concern document(s) or information included:			
<p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98-International Search Report (PCT/ISA/210) w/ 3 documents</p> <p>12. <input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A FIRST preliminary amendment.</p> <p>14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input checked="" type="checkbox"/> Other items or information:</p> <p>1.) Small Entity Statement</p> <p>2.) PCT Request</p> <p>3.) International Preliminary Examination Report (PCT/IPEA/409)</p> <p>4.) Zero (0) sheets of Formal Drawings</p>			

U.S. APPLICATION NO (if known, see 37 CFR 1.5) <b>09/006455</b>		INTERNATIONAL APPLICATION NO PCT/SE99/01729		ATTORNEY'S DOCKET NUMBER 4013-0158P	
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21. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. .... <b>\$1,000.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$860.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. .... <b>\$710.00</b>  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$690.00</b>  International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). .... <b>\$100.00</b> <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>	<b>CALCULATIONS      PTO USE ONLY</b>           <div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>1000.00</span> </div>													
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>0</span> </div>													
<table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:15%;">CLAIMS</th> <th style="width:20%;">NUMBER FILED</th> <th style="width:20%;">NUMBER EXTRA</th> <th style="width:20%;">RATE</th> </tr> </thead> <tbody> <tr> <td>Total Claims</td> <td>14 - 20 =</td> <td>0</td> <td>X \$18.00</td> </tr> <tr> <td>Independent Claims</td> <td>1 - 3 =</td> <td>0</td> <td>X \$80.00</td> </tr> </tbody> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	Total Claims	14 - 20 =	0	X \$18.00	Independent Claims	1 - 3 =	0	X \$80.00	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>0</span> </div>	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE											
Total Claims	14 - 20 =	0	X \$18.00											
Independent Claims	1 - 3 =	0	X \$80.00											
MULTIPLE DEPENDENT CLAIM(S) (if applicable) Yes <input checked="" type="checkbox"/> + \$270.00	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>270.00</span> </div>													
<b>TOTAL OF ABOVE CALCULATIONS =</b>	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>1270.00</span> </div>													
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>-635.00</span> </div>													
<b>SUBTOTAL =</b>	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>635.00</span> </div>													
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>0</span> </div>													
<b>TOTAL NATIONAL FEE =</b>	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>635.00</span> </div>													
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>40.00</span> </div>													
<b>TOTAL FEES ENCLOSED =</b>	<div style="display: flex; justify-content: space-between;"> <span>\$</span> <span>675.00</span> </div>													
	Amount to be: refunded \$ charged \$													

a. ☒ A check in the amount of \$ 675.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees.  
 A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

Send all correspondence to:  
**Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292**  
**P.O. Box 747**  
**Falls Church, VA 22040-0747**  
**(703)205-8000**

**Date: March 30, 2001**

By Joe McKinney Muncy  
 Joe McKinney Muncy, #32,334

/cqc

09/806455

PATENT

4013-0158P

532 Rec'd PCT/PTO 30 MAR 2001

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: ADOLFSSON, Erik et al. Conf.:  
Int'l. Appl. No.: PCT/SE99/01729  
Appl. No.: New Group:  
Filed: March 30, 2001 Examiner:  
For: BIOACTIVE COMPOSITE MATERIALS AND METHOD OF  
PRODUCING THE SAME

PRELIMINARY AMENDMENT

**BOX PATENT APPLICATION**

Assistant Commissioner for Patents  
Washington, DC 20231

March 30, 2001

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

**AMENDMENTS**

**IN THE SPECIFICATION:**

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/SE99/01729 which has an International filing date of September 29, 1999, which designated the United States of America.--

**IN THE CLAIMS:**

Please amend the claims as follows:

5. (Amended) Method according to claim 1, characterized in that said composite material comprises hydroxyapatite and/or other apatite in a concentration of 5-80 vol%, preferably 10-50 vol% and even more preferred 25-45 vol%.

6. (Amended) Method according to claim 1, characterized in that said closing of the system and applying of pressure takes place at temperatures below 900°C, for ceramic based composites preferably below 800°C, even more preferred below 700°, and for more metal based composites preferably below 500°C.

7. (Amended) Method according to claim 1, characterized in that said densification of the material is driven to an end temperature above 900°C, preferably above 1000°C and even more preferred above 1100°C, for ceramic based composites, or 500-800°C, preferably 600-800°C for metal based composites, and an end pressure above 100 Mpa, preferably up to 200 Mpa.

8. (Amended) Method according to claim 1, characterized in that said applying of pressure is performed as a partial applying of pressure, before an end temperature for the densification is reached, and before commencing decomposition of apatite phase, whereby a part of pressure of 0.2-10 Mpa is applied.

9. (Amended) Method according to claim 1, characterized in that said densification of the material is performed stepwise, whereby a first part pressure is applied, preferably of about 0.2-5 Mpa, and is maintained up to a first temperature, whereafter a second part pressure is applied, preferably of about 1-10 Mpa, and is maintained up to a second temperature, whereafter a possible further is applied, or an end pressure and an end temperature is applied.

10. (Amended) Method according to claim 1, characterized in that one or more helping agents are added to a barrier layer at densification by hot isostatic pressing or to a powder bed at densification by over pressure sintering, in order to further suppress unwanted reactions, like decomposition and oxidation.

12. (Amended) Bioactive composite material, comprising apatite, for dental or orthopaedic use, which comprises groups with a tendency for decomposition (e.g. vaporization), characterized in that it has been produced by to a method according to claim 1.

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application. The claims have also been amended to delete multiple dependencies and to place the application into better form for examination. Entry of the present amendment and favorable action on the above-identified application are earnestly solicited.

Attached hereto is a marked-up copy of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Joe McKinney Muncy  
Joe McKinney Muncy, #32,334

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4013-0158P

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Falls Church, VA 22040-0747  
(703) 205-8000

Attachment: Version With Markings Showing Changes Made

(Rev. 01/22/01)

**VERSION WITH MARKINGS SHOWING CHANGES MADE**

The specification has been amended to provide cross-referencing to the International Application.

The claims have been amended as follows:

5. (Amended) Method according to [any of the preceding claims]claim 1, characterized in that said composite material comprises hydroxyapatite and/or other apatite in a concentration of 5-80 vol%, preferably 10-50 vol% and even more preferred 25-45 vol%.

6. (Amended) Method according to [any of the claims 1-5]claim 1, characterized in that said closing of the system and applying of pressure takes place at temperatures below 900°C, for ceramic based composites preferably below 800°C, even more preferred below 700°, and for more metal based composites preferably below 500°C.

7. (Amended) Method according to [any of the preceding claims]claim 1, characterized in that said densification of the material is driven to an end temperature above 900°C, preferably above 1000°C and even more preferred above 1100°C, for ceramic based composites, or 500-800°C, preferably 600-800°C for metal based composites, and an end pressure above 100 Mpa, preferably up to 200 Mpa.

8. (Amended) Method according to [any of the preceding claims]claim 1, characterized in that said applying of pressure is performed as a partial applying of pressure, before an end temperature for the densification is reached, and before commencing decomposition of apatite phase, whereby a part of pressure of 0.2-10 Mpa is applied.

9. (Amended) Method according to [any of the preceding claims]claim 1, characterized in that said densification of the material is performed stepwise, whereby a first part pressure is applied, preferably of about 0.2-5 Mpa, and is maintained up to a first temperature, whereafter a second part pressure is applied, preferably of about 1-10 Mpa, and is maintained up to a second temperature, whereafter a possible further is applied, or an end pressure and an end temperature is applied.

10. (Amended) Method according to [any of the preceding claims]claim 1, characterized in that one or more helping agents are added to a barrier layer at densification by hot isostatic pressing or to a powder bed at densification by over pressure sintering, in order to further suppress unwanted reactions, like decomposition and oxidation.



12. (Amended) Bioactive composite material, comprising apatite, for dental or orthopaedic use, which comprises groups with a tendency for decomposition (e.g. vaporization), characterized in that it has been produced by to a method according to [any of the above claims]claim 1.

# BIOACTIVE COMPOSITE MATERIALS AND METHOD OF PRODUCING THE SAME

## TECHNICAL FIELD

- 5 The present invention relates to optimal conditions for producing bioactive materials containing compounds (phases) which have a tendency for decomposition at the production of the material. The invention is specifically relating to materials for use as resistant medical implants.

## 10 BACKGROUND OF THE INVENTION

- Materials which are used in bioactive contexts often contain phases of differing character. Specifically, any of the included phases may have a large tendency for decomposition at the production, which for metals and especially ceramics take place at an elevated temperature. This commencing thermally activated decomposition may have a
- 15 directly negative effect on the end product, for example by formation of gaseous compounds which form pores that acts as defects, especially from a strength point of view, or by contributing to the formation of new unwanted phases. A related effect is that decomposition of the phase with a tendency for decomposition is catalysed by the presence of another phase, for example an oxide, which leads to decomposition at temperatures
- 20 which considerably decrease those for the corresponding pure material with a tendency for decomposition. The presence of an oxide or metal in the bioactive composite material is necessary in order to improve the mechanical properties in relation to pure apatite.
- 25 Other related aspects, which however do not concern the basic area of the present application, are e.g. treated, besides in the literature, in the following patents/patent applications: US 3 789 900, DE 330122, US 4 149 893, US 4 957 674, US 4 599 085, DE 29 28 007 A1 and JP 62-142 565.

## 30 DESCRIPTION OF THE INVENTION

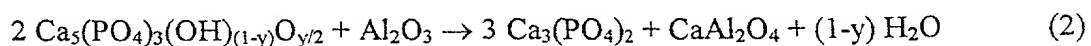
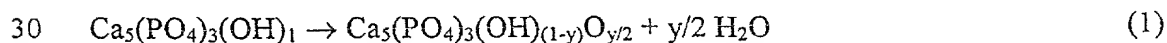
- The present invention relates to composite materials, and a method of producing the same, which material comprises at least one chemically less stable phase, and relates specifically to resistant ceramic implant materials.
- 35 The object of the invention is to provide bioactive materials, especially implant materials, with a supporting function in dental or orthopaedic applications with optimal properties, by use of production methods where special consideration has been taken to the

bioactive, but chemically less stable, phases included. Key aspects of the invention concern reactions between non active and active (bio-functional) phase, and how these unwanted reactions may be minimised or eliminated or controlled. A new theoretical model has been developed on the decomposition in composite materials, which corresponds to the obtained results according to the present invention.

According to the invention there is thus presented a material and a method of producing the same, in accordance with the enclosed patent claims.

The composite material according to the invention comprises apatite in contents below 90 vol-%, preferably 5-80 vol-%, even more preferred 10-50 vol-% and most preferred 25-45 vol-%. The apatite phase may be pure hydroxyapatite or mixtures of apatite phases, i.e. hydroxyapatite and fluorapatite. The bioinert base mass in the composite material is preferably a construction ceramic, preferably one or more oxides, e.g. aluminium oxide, zirconium oxide and/or titanium oxide. The content of construction ceramic may be 10-95 vol-%, preferably 40-95 vol-% and more preferably 55-85 vol-% and is suitably dominant in the material. As an alternative, the bioinert base mass may be a construction metal in the same concentrations, preferably a Fe or Co-Cr based or Ti, Ta or Zr based construction metal. Low contents (preferably below 10 vol-%) of other phases may also exist besides apatite and bioinert base mass.

It has surprisingly been discovered, in connection with the invention, that the reaction mechanism for decomposition of apatite in the oxide-hydroxyapatite system does not take place according to what is conventionally presented in the literature, but takes place in two steps, where OH groups in hydroxyapatite, OHAp =  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ , first leaves the structure, leaving vacancies in the same. When the number of vacancies exceeds a certain critical level, defect OHAp may continue to react with surrounding compounds (e.g.  $\text{Al}_2\text{O}_3$ ) which catalyse the decomposition. The two steps of the reaction are



This type of decomposition takes place at densification/sintering of the material. By changing the equilibrium reactions decomposition may however be avoided, which may be done in three principally different ways, namely by decreasing the temperature in a

closed system, increasing the pressure and/or deliberately introducing the compounds which the active compound strives to decompose to. This leads to that a low sintering temperature should be used, that closing must take place early, before the actual sintering process begins, and that an outer mechanical pressure should be applied to the capsule before the densification begins, at the densification/calcination/sintering of material according to the invention. Furthermore, the initially applied pressure, i.e. the pressure which is applied before the densification begins, should be maintained as a minimum pressure level during the continued densification, i.e. the pressure should normally not be allowed to decrease below the initial pressure during the continued densification/sintering, but should instead be gradually increased.

In the method according to the invention, the powder mixture of apatite and oxide or metal is suitably initially shaped to a raw press body by for example cold isostatic pressing (CIP) or other forming method. Thereafter, the raw press body is densified/sintered, suitable methods being hot isostatic pressing (HIP) or sintering in a closed chamber with possibilities for gas overpressure, overpressure sintering (GPS, gas pressure sintering). At hot isostatic pressing, the raw press body is placed in a pre-shaped capsule, whereafter the capsule is closed. The surrounding gas applies a pressure on the capsule which transmits the pressure to the raw press body itself, which is densified. At overpressure sintering on the contrary, the raw press body is in direct contact with the gas. In both sintering techniques, some type of barrier layer or powder bed may be used, which surrounds the raw press body. To these help layers there may, according to the invention, advantageously be added compounds, e.g. hydrates, which decompose and form compounds which counteract either the decomposition of apatite, or compounds which prevent the metal in the case of metal-apatite composition from being chemically attacked.

According to the invention, closure of the system/capsule and applying of pressure should be performed before commencing substantial decomposition of apatite phase, i.e. at temperatures which are considerably lower than the end temperature for the sintering. In some cases the applying of pressure may be performed already at room temperature, and should generally be performed at temperatures below 900 °C, for ceramic based composites preferably below 800 °C, even more preferred below 700 °C, and for metal based composites preferably below 500 °C. This initial applying of pressure may be complete or partial, i.e. the level of the applied pressure may be equal to the end pressure or may be less than the end pressure. The end pressure for HIP is usually very high, most often over 100 MPa, up to 200 MPa or even higher. At sintering in a closed cham-

ber the gas pressure is usually 100-200 atm at the most, i.e. 10-20 MPa. An initial pressure may be 10 MPa or below, down to about 0.2 MPa. At lower temperatures the purpose of such a low initial pressure is primarily to prevent the capsule material from expanding from increased pressure due to the temperature enhancement (according to the perfect gas law) or by deliberately added compounds begin to decompose to gaseous compounds, preferably steam. An initial part pressure at any level between 0.2 MPa and the end pressure is however also conceivable. Exactly which pressure is used is chosen depending on the type of composite system, the type of powder (grain size and morphology), the amount being processed, deliberately added extra decomposing compounds and the type of capsule and sintering technique. The end temperature is, for oxide based materials, typically at least 900 °C, usually at least 1000 °C and most often at least 1100 °C. For metal based materials, the end temperature is lower, typically about 500-800 °C, usually 600-800 °C. The end pressure and end temperature is usually maintained for about 1-2 hours.

According to one aspect of the invention the applying of pressure and the temperature enhancement is performed stepwise. The purpose is to apply an increased pressure stepwise, as is needed in connection with the temperature enhancement. A first initial pressure, which is applied already at room temperature and which may be kept at a level of e.g. 0.2-5 MPa, may thereby have the purpose of stabilising the capsule. When the temperature thereafter is additionally increased, the pressure in the capsule increases in accordance with the perfect gas law. At temperature levels below the temperature level for commencing decomposition of apatite phase there is also a commencing decomposition of possibly additionally added helping agents in the form of decomposing compounds (see also below), which also leads to an increase of the pressure in the capsule. Altogether there is therefore required an increased pressure level, of e.g. about 1-10 MPa, as a counter pressure. Finally, when temperature levels are reached where the material of the raw press body itself, the apatite phase, may begin to decompose (see previously mentioned temperature levels) the desired end pressure is applied in order to prevent such decomposition. The temperature is then increased to the desired end temperature and is maintained for the sintering. Exactly how the stepwise pressure application is performed depends on the type of composite system, the type of powder (grain size and morphology), the amount being processed, deliberately added extra decomposing compounds and the type of capsule and sintering technique.

The use of hot isostatic pressing (HIP) in connection with the production of ceramics is of course generally known per se, and has been described also for the oxid-apatite sys-

tem, namely in Swedish patent 465 571. In those contexts there is however not described the capsuling performance itself – closing and early applying of pressure or addition of helping agents in the barrier layer – but only the temperature and pressure at the densification itself. In order to be able to safeguard against decomposition and unwanted reactions at the sintering, the step which precedes the actual hot isostatic pressing (the densification) must also be considered, and be performed according to the present invention, where the temperature at the closing and the temperature at the applying of pressure on the capsule, (or gas pressure in the case of GPS) in the temperature interval before the actual sintering, is adapted to the tendency of decomposition of the existing phases. The use of isostatic compression only as a part of the process for porous apatite, as in WO-A1-9410100, is not working for formation of dense and resistant apatites, and especially not for highly resistant biocomposites of apatite, where decomposition takes place at considerably lower temperatures than for pure apatite, since the decomposition is being catalysed by oxides. See results in example 1. The applying of pressure must take place depending on the tendency of decomposition for different oxide-apatite systems at temperatures below the ones given in WO-A1-9410100.

According to another aspect of the invention, there may be deliberately added an additional decomposing compound in the closed system, which generates a compound that the composite system (mainly the apatite phase) tends to decompose into. Decomposition of the composite material is thereby additionally counteracted. In an especial embodiment there is accordingly also used, besides an early closure and an early stepwise applying of pressure, addition of a decomposing help compound in powder form, which early forms the phases or any phase which the functional phase strives to decompose into in the actual component, whereby the decomposition reaction is driven to a decreased decomposition. In the case of a composite material containing metal and a functional phase (apatite), there may be added a second helping agent which decreases the metal reactions – mainly oxidation. In these cases where densification generally takes place at a lower temperature than for ceramics it is often the metal which is the more reactive phase. In these cases the helping agent is advantageously fine-grained metal powders, e.g. fine-grained iron powder or fine-grained titanium powder, which reduces the oxygen content in the gas environment surrounding the composite material. Help compounds against decomposition of the active phase and helping agents for the preservation of the metal phase may advantageously be added to a barrier layer or powder bed which may surround the component at the processing. In order to prevent decomposition of apatite phases, different types of hydrates which easily give off hydroxyl groups and forms steam and other groups (carbonate, phosphate etc.) may be incorpo-

rated as helping agents in a barrier layer or powder bed. Material which is used as a helping agent in this way may generally be a hydrate (for example hydrated cement or salt with crystal water) which gives off water at temperatures which are lower than the temperatures at which decomposition reactions in the oxide-apatite system commences, i.e. at temperatures of at least below 900 °C, preferably below 800 °C and even more preferred below 600 °C. The concentration of helping agent, when such is used, is generally low and is adapted for the system in question and the amount of material which is to be processed. In a powder bed the concentration of helping agent is typically less or equal to 10 vol-%, in a barrier layer less than ca 5 vol-%.

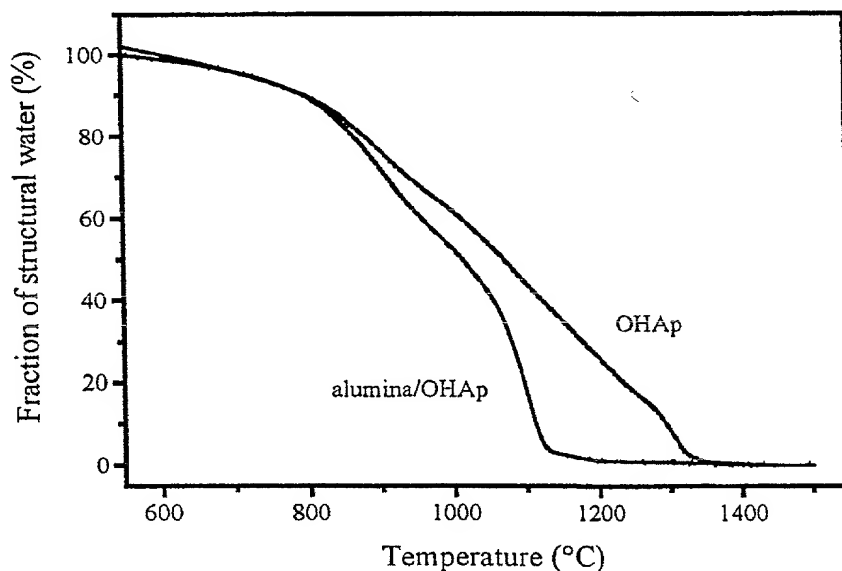
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The invention is additionally described by a number of embodiment examples.

#### Example 1

In the figure below there is shown an example of how the departure of water takes place from pure hydroxyapatite (OHAp) and from hydroxyapatite in a composite (aluminium oxide with 60 vol-% hydroxyapatite).

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The reason for the difference in water departure is decomposition, which for the composite takes place in sequential steps according to reaction 1 and 2 (see the describing text above), and which for pure hydroxyapatite only takes place according to reaction 1. The departure of hydroxyl groups is accelerated by the presence of oxide. The graphs have been plotted by thermogravimetric analysis in a TG apparatus of the brand Seta-

20

ram TAG24. The departure of water is standardised according to the same content of hydroxyapatite.

#### Example 2

- 5 Tetragonal stabilised zirconium oxide powder (TZ) including 45 vol-% hydroxyapatite powder, HA, was hot isostatic pressed with differing closure and applying of pressure but with the same end parameters, namely 1200 °C and 200 MPa for 1 h. In the first case (TZ-HA I), the capsule material of glass was closed at 900-950 °C, and the full pressure was applied at 1150 °C. In the second case (TZ-HA II), the closing took place  
10 at room temperature and with an overpressure of about 5 atm up to 650 °C, where 80 atm was applied. At 800 °C there was applied a pressure of 160 MPa which after temperature rise to the top temperature gave the end pressure 190 MPa. An analysis of the micro structure with a scanning electron microscope shows that TZ-HA I contains a number of very small pores and that a part of the tetragonal phase has transferred into a  
15 cubic phase at the same time as HA has decomposed into TCP,  $\text{Ca}_3(\text{PO}_4)_2$ . The pores have, with high probability, derived from departed OH groups. For TZ-HA II there is obtained a completely dense material with a maintained tetragonal structure, which is beneficial for strength and resistance to rupture. As a comment, decomposition of HA to TCP – which deliberates CaO and which contributes in the phase transformation of  
20 tetragonal phase into cubic phase – is hard to detect in a more coarse micro structure, since the decomposition reactions take place in the border line between TZ and HA, the amount reacting depending on micro structure (distribution of TZ grains and HA grains and the size of the grains).

#### Example 3

- 25 Titanium dioxide and hydroxyapatite (HA) was mixed and was blended in the grinding in a ball mill with Sialon mill bodies and iso-propanol for solvent, during 4 days. The solvent was driven off in an oven in a closed hood at 90 °C and was finally dried at 450 °C during 2 h. The content of HA was 30 vol-%. Samples were hot isostatic pressed  
30 with differing closure and applying of pressure. In test A closure took place at room temperature and a pressure of 3 atm overpressure was applied, which was maintained up to 700 °C, where the end pressure of 160 MPa was applied and the temperature was raised to 900 °C and was maintained constant for 1 h. In test B closure and final applying of pressure, 160 MPa, took place directly at 900 °C and was maintained for 1 h.  
35 Samples from test A contains the desired phases rutile and HA, while the result from test B shows a certain decomposition and formation of titanate,  $\text{CaTiO}_3$ , together with TCP,  $\text{Ca}_3(\text{PO}_4)_2$ . No porosity worth mentioning has been detected. Here too, the possi-



bility of detection through phase analysis with X-ray diffraction depends on HA and micro structure. The tendency of titanate formation is however obvious. Generally, decomposition of HA is hard to detect when the content of HA is less than about 20 vol-% in the composite.

5

#### Example 4

Aluminium oxide was mixed with hydroxyapatite, HA, according to the method described in Example 2. The content of HA was 45 vol-%. Samples were densified either with hot pressing (HP) at 1200 °C, 25 MPa during 2 h, or by hot isostatic pressing (HIP) with full applying of pressure, 160 MPa at 700 °C, and a temperature rise to 1200 °C, maintained for 2 h. In the hot pressed samples there is shown decomposition of HA to TCP,  $\text{Ca}_3(\text{PO}_4)_2$ , while the hot isostatic pressed samples are showing the correct phases containing aluminium oxide and HA.

#### Example 5

A fine-grained steel powder, 316L, is mixed with 40 vol-% hydroxyapatite, HA according to example 2, with the difference that the driving off of solvent takes place at vacuum at 200 °C. The material, a cold isostatic pressed body, is placed in a capsule intended for hot isostatic pressing, which is closed under vacuum. An end pressure of 160 MPa is applied at 600 °C during 1 h. Analysis of micro structure (SEM) and phase analysis (X-ray diffraction) show that a completely dense material with maintained HA phase is present in the end product. In the barrier layer of boron nitride there had been added an additional fine-grained metal powder consisting of 316 L in a concentration of 10 vol-%, which was finely powdered by being blended in the grinding during 2 days.

## CLAIMS

1. Method of producing a bioactive composite material, comprising apatite, for dental or orthopaedic use, which material comprises groups with a tendency for decomposition (e.g. vaporisation), where a densification of the material is performed at high temperatures under pressure, characterised in that the densification is performed in a closed system where applying of pressure partially or completely takes place before an end temperature for the densification is reached, and before commencing substantial decomposition of apatite phase.
2. Method according to claim 1, characterised in that said groups with a tendency for decomposition are hydroxyl, carbonate, phosphate, halogen or a combination thereof.
3. Method according to any of the preceding claims, characterised in that one phase in the material comprises a construction ceramic, preferably an oxide, most preferably aluminium oxide, zirconium oxide or titanium oxide, in a concentration of 10-95 vol-%, preferably 40-95 vol-% and even more preferred 55-85 vol-%.
4. Method according to any of claims 1-2, characterised in that one phase in the material comprises a construction metal, preferably Fe or Co-Cr based or Ti, Ta or Zr based, in a concentration of 10-95 vol-%, preferably 40-95 vol-% and even more preferred 55-85 vol-%.
5. Method according to any of the preceding claims, characterised in that said composite material comprises hydroxyapatite and/or other apatite in a concentration of 5-80 vol-%, preferably 10-50 vol-% and even more preferred 25-45 vol-%.
6. Method according to any of claims 1-5, characterised in that said closing of the system and applying of pressure takes place at temperatures below 900 °C, for ceramic based composites preferably below 800 °C, even more preferred below 700 °C, and for metal based composites preferably below 500 °C.
7. Method according to any of the preceding claims, characterised in that said densification of the material is driven to an end temperature above 900 °C, preferably above 1000 °C and even more preferred above 1100 °C, for ceramic based composites, or 500-800 °C, preferably 600-800 °C for metal based composites, and an

end pressure above 100 MPa, preferably up to 200 MPa.

- 5 8. Method according to any of the preceding claims, characterised in that said applying of pressure is performed as a partial applying of pressure, before an end temperature for the densification is reached, and before commencing decomposition of apatite phase, whereby a part pressure of 0.2-10 MPa is applied.
- 10 9. Method according to any of the preceding claims, characterised in that said densification of the material is performed stepwise, whereby a first part pressure is applied, preferably of about 0.2-5 MPa, and is maintained up to a first temperature, whereafter a second part pressure is applied, preferably of about 1-10 MPa, and is maintained up to a second temperature, whereafter a possible further is applied, or an end pressure and an end temperature is applied.
- 15 10. Method according to any of the preceding claims, characterised in that one or more helping agents are added to a barrier layer at densification by hot isostatic pressing or to a powder bed at densification by over pressure sintering, in order to further suppress unwanted reactions, like decomposition and oxidation.
- 20 11. Method according to claim 10, characterised in that said helping agent is a fine-grained metal powder and/or an easily decomposing hydrate.
- 25 12. Bioactive composite material, comprising apatite, for dental or orthopaedic use, which comprises groups with a tendency for decomposition (e.g. vaporisation), characterised in that it has been produced by to a method according to any of the above claims.

# SMALL ENTITY DECLARATION

APPLICANT OR PATENTEE Doxa Certex Aktiebolag

SERIAL NO. New ☐ PATENT NO. March 30, 2001 ATTORNEY'S DOCKET NO. 4013-0158P

Check one of blocks or 2.)

1. ☐ FILED OR ISSUED

2. ☐ SUBMITTED HERewith

FOR Bioactive composite materials and method of producing the same

(Insert Title)

I(we) hereby declare that I(we) am(are) entitled to the benefit of small entity status with respect to the above-identified application or patent for purposes of paying reduced fees under 35 USC 41(a) & (b) to the U.S. Patent and Trademark Office.

- ☐ A. INDEPENDENT INVENTOR  
I(we) qualify as (an) independent inventor(s) as defined in 37 CFR 1.9(c).
- ☐ B. INDIVIDUAL NON-INVENTOR  
I would qualify as an independent inventor as defined in 37 CFR 1.9(c) if I had made the invention.

☒ C. SMALL BUSINESS CONCERN  
I am ☒ THE OWNER ☒ AN OFFICIAL of the small business concern identified below and am empowered to act on behalf of the concern. The concern qualifies under 37 CFR 1.9(d) and 13 CFR 121.3-18. Rights under contract or law have been conveyed to and remain with the concern and are exclusive unless a checkmark is placed here ☐. All other rights belong to small entities as defined in 37 CFR 1.9.

☐ D. NON-PROFIT ORGANIZATION  
I am an official empowered to act on behalf of the non-profit organization identified below. The organization qualifies under 37 CFR 1.9(e), sub-section: ☐ (1) ☐ (2) ☐ (3) ☐ (4). Rights under contract or law have been conveyed to and remain with the organization and are exclusive unless a checkmark is placed here ☐. All other rights belong to small entities as defined in 37 CFR 1.9.

I(we) acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I(we) declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

A. INDEPENDENT INVENTOR(S) B. INDIVIDUAL NON-INVENTOR(S)

Name	Signature	Date

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Name of Concern or Organization Address

By Peter Bramberg Peter Bramberg  
 Name of Person Signing Signature  
PETER BRAMBERG President 20 February -2001  
 Title Date

# COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

ATTORNEY DOCKET NO.  
4013-0158P

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the invention entitled:

"Bioactive composite materials and method of producing the same"

, the specification  
of which

(check one)

☐ is attached hereto.

☒ was filed on September 29, 1999 as

Application Serial No. PCT/SE99/01729

and was amended on \_\_\_\_\_  
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows:

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below:

Prior Foreign Application(s)			Priority Claimed	
<u>9803385-5</u>	<u>Sweden</u>	<u>2 October, 1998</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u>                    </u>	<u>                    </u>	<u>                    </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u>                    </u>	<u>                    </u>	<u>                    </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u>                    </u>	<u>                    </u>	<u>                    </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u>                    </u>	<u>                    </u>	<u>                    </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months Prior To The Filing Date of This Application:

Country	Application No.	Date of Filing (Day/Month/Year)
<u>                    </u>	<u>                    </u>	<u>                    </u>
<u>                    </u>	<u>                    </u>	<u>                    </u>

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>PCT/SE99/01729</u>	<u>29 September, 1999</u>	<u>pending</u>
(Application Serial No.)	(Filing Date)	(Status — patented, pending, abandoned)
<u>                    </u>	<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)	(Status — patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and/or an international application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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